REMARKS

Upon entry of the instant amendment, claim 116 will be canceled without prejudice or disclaimer of the subject matter recited therein, and claim 105 will be amended. Claims 91-115 and 117-139 will remain pending.

Claim 105 has been amended to recite a method for preparing a wound-healing promoting material which comprises extracorporeally contacting at least living leukocytes contained in a liquid portion with a sheet-shaped porous body to trap the at least living leukocytes on surfaces of pores of the porous body, and substantially not trapping the liquid portion including fibrinogen on the surfaces. The amendment of claim 105 is in accordance with the disclosure in Applicants' originally filed application including, for example, page 13, third full paragraph, wherein it is disclosed (with emphasis provided in bold) that:

> The sheet-like porous body used in the present invention is made of a material that can trap at least blood cells, such as leukocytes and/or platelets, from a cell suspension of blood and the like. The sheet-like porous body preferably functions as a filter layer. Specifically, the sheet-like porous body is capable of separation in a manner such that the porous body traps at least blood cells, such as leukocytes and/or platelets, or growth factors **but does not trap the liquid portion, when the cell suspension is brought into contact with or passed through the sheet-like porous body**. Such separation includes not only size-based separation, but also separation based on cell affinity (e.g., adsorptivity) to the surface of the material.

Moreover, attention is directed, for example, to page 19, second full paragraph, wherein it is disclosed (with emphasis provided in bold) that:

> The wound-healing promoting material of the present invention can further comprise fibrins. **A fibrinogen solution for preparing fibrins is not particularly limited, and a solution commercialized as a pharmaceutical preparation can be used. Also, a liquid that is recovered as drainage from a sheet-like porous material when blood is employed as a blood cell suspension is centrifuged, the centrifugation product can be concentrated, and the concentrate can be used as a fibrinogen solution.** When fibroblasts are contained, cells may be previously embedded in fibrins. Also, only cells may be seeded into fibrins later. Incorporation of fibrins into the wound-healing promoting material facilitates the fixation thereof

at the wound site. In addition, other growth factors contained in fibrin gel can improve the effects of promoting wound healing.

Accordingly, Applicants' originally filed application supports the claimed subject matter including substantially not trapping the liquid portion including fibrinogen on the surfaces. Therefore, no new matter should be considered to be included in the amendment herein.

Entry of this amendment after final rejection is appropriate, because the amendment seeks to address issues added by the rewording the rejection including the new use of Faraday. The amendment further seeks to reduce the issues for appeal by removing at least one or more rejections, and should be considered to place the application in condition for allowance.

Accordingly, entry of this amendment after final rejection, and reconsideration and allowance of the application are respectfully requested.

Information Disclosure Statement

Applicants express appreciation for the confirmation of consideration of Applicants' Information Disclosure Statement filed May 14, 2009 by including an initialed copy of the Form PTO-1449 with the Final Office Action.

Response To Maintaining of Restriction Requirement

The Office Action has maintained the restriction requirement with claims 105-120 and 137-139 being under prosecution, and claims 91-104 and 121-136 standing withdrawn from consideration.

Applicants request rejoinder of the non-elected subject matter following allowance of the elected claims.

Response To Withdrawal of Rejections and Instituting of New Rejections Under 35 U.S.C. 102(b) and 103(a)

Applicants express appreciation for the withdrawal of the anticipation rejection based upon U.S. Patent No. 5,651,966 to Read et al. (hereinafter "Read") with support by Wakelyn et al. (handbook of Fiber Chemistry, 1998 – hereinafter "Wakelyn"), and the obviousness rejections based upon Read in light of support by Seagull et al. (J. Cotton Science – hereinafter "Seagull"), or Read, Seagull, and U.S. Patent No. 5,407,581 to Onodera et al. (hereinafter "Onodera"), and Jan et al. (J. General Physiology, 1973 – hereinafter "Jan").

Moreover, the rejection based upon Read and support in view of U.S. Patent Publication No. US 2003/007957 to Britton et al. (hereinafter "Britton") is not repeated in the Office Action, but is modified to include another document, i.e., Faraday et al. (Anesthesiology 2001; 94:145-151 – hereinafter "Faraday").

The Office Action has set forth the following art based rejections:

(a) Claims 105-107, 115-117 and 120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Read in further view of Britton with support by Wakelyn, Seagull and Faraday.

(b) Claims 105-120 and 137-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Read, Britton, and supporting references as applied to claims 105-107, 115-117 and 130, and further in view of Onodera in light of support of Jan.

In response to the rejections set forth in the Final Office Action, Applicants point out that Applicants' independent claim 105 is directed to a method for preparing a wound-healing promoting material which comprises extracorporeally contacting at least living leukocytes contained in a liquid portion with a sheet-shaped porous body to trap the at least living

leukocytes on surfaces of pores of the porous body, and substantially not trapping the liquid portion including fibrinogen on the surfaces. Thus, according to Applicants' recited subject matter, a sheet-shaped porous body wherein at least living leucocytes are trapped is prepared to obtain a wound-healing promoted material, and the method includes substantially not trapping the liquid portion including fibrinogen on the surfaces. According to the claimed subject matter, living leukocytes are physically trapped and retained at a porous region, and therefore the activity of living cells is maintained. In contrast, Read uses fixed-dried platelets as compared to living leukocytes as recited in Applicants' independent claim 105 and claims dependent therefrom.

Applicants once again point out that the differences between Read and Applicants' claimed subject matter is readily evident from the full disclosure of Read. For example, in the Summary of the Invention section of Read, it is disclosed that there are three aspects to the Read invention, and each of these three aspects include using "fixed-dried human blood platelets", as follows (with emphasis added):

> A first aspect of the present invention is **fixed-dried human blood platelets** which, upon reconstitution: (a) adhere to thrombogenic surfaces; (b) do not adhere to non-thrombogenic surfaces; (c) undergo shape change (spreading) upon adhering to a thrombogenic surface; (d) adhere to one another to form a hemostatic plug upon adhering to a thrombogenic surface; and (e) release their granular contents, such as after stimulation and/or spreading (e.g., after receiving a physiological stimulation which would ordinarily cause a metabolically active, live or fresh platelet to release its granular contents, such as contacting wounded tissue).
>
> A second aspect of the present invention is a pharmaceutical formulation comprised of **a fixed-dried blood platelets preparation**. The fixed-dried blood platelet preparation comprises fixed-dried human blood platelets having the characteristics set forth above.
>
> A third aspect of the present invention is a method of **fixing blood platelets to produce fixed-dried blood platelets** having the characteristics set forth above, and the platelets so produced. The method comprises contacting the platelets to a fixative such as formaldehyde, paraformaldehyde, glutaraldehyde, or permanganate (e.g., by mixing the

> platelets with a solution thereof) for a time sufficient to fix or stabilize the platelets but insufficient to cause loss of the characteristics enumerated above. The platelets are then dried to yield fixed-dried blood platelets having the characteristics set forth above.

Thus, in Read, **fixed-dried platelets having no cell activity** are used in the preparation method. In contrast, according to Applicants' claimed subject matter, by preparing a wound-healing promoting material which comprises extracorporeally contacting at least living leukocytes with a sheet-shaped porous body to trap the at least living leukocytes on surfaces of pores of the porous body, there is able to be obtained a wound-healing promoting material wherein living leukocytes are physically trapped in the porous body. Therefore, cell activity is not lost according to Applicants' method of preparing a would-healing promoting material as is the case with Read's fixed-dried platelets. The living leucocytes on Applicants' prepared wound-healing promoting material can be directly contacted with a wound region, and thus wound-healing function in the living body can. be promoted. The claimed subject matter is clearly different from Read's method of preparation, and there is no teaching or suggestion in Read to arrive at Applicants' claimed method of preparing a wound-healing promoting material.

Britton does not overcome the deficiencies of Read because one having ordinary skill in the art would not have combined the disclosures of Read and Britton. However, even if for the sake of argument the disclosures were combined, Applicants' claimed subject matter would not be at hand. For example, Britton discloses (with emphasis added) in paragraph [0018] the difference between his invention and the prior art:

> **While the prior art activates, isolates and employs potentially unstable growth factors and independently applies said activated factors directly to the wound**, the present invention contemplates the application of an autologous derived platelet rich plasma concentrate directly to the wound surface, thereby requiring the platelet-rich plasma concentrate to interface directly at the site of injury. It is essential in the present invention to note that it is the injured tissue

that begins or initiates a sustainable and natural physiologic activation of the plasma-rich plasma concentrate, not the external and artificial activation with bovine-derived products in the prior art. Therefore, it has been a long-felt need to step back from an elemental factor-by-factor analysis and application of single or multiple growth factor elements. **Instead, the present invention encompasses a broader and more comprehensive approach to wound care whereby a large majority of the necessary wound healing elements and scaffolding such as platelets, platelet cell membranes, fibrin, and white blood cells are provided in a concentrated form.** The present invention represents a departure from the present trend since it is premised on the understanding that the collection of many wound healing elements serves a higher purpose when compared to the individual, incremental approach. Indeed, the present invention contemplates a synergistic effect of all components. Surprisingly, the present invention actually minimizes inflammation and the corresponding pain and swelling incident to a prolonged inflammatory response. The present invention is a more physiologically relevant regimen whereby a treated patient is not subjected to simply the immediate benefit of exogenous, artificial, and pre-activated autologous platelet derived wound care agents. Instead, the patient will enjoy a sustainable and directly acting reservoir effect incident to the auto-activation of platelet rich plasma. The present invention also contemplates the use of a carrier substrate in connection with the auto-activated platelet-rich plasma concentrate. The carrier substrate, in combination with the platelet-rich plasma concentrate, serves as a malleable structural matrix. This structural matrix, and the addition of potential preservatives and/or additives thereto, better enables the user to store, apply, handle, or manipulate the size of the tissue graft to a particular wound size and better enables the patient to go longer periods of time between bandage changes.

Thus, Britton specifically discloses that the various components are placed into his matrix by suspending the platelet-rich plasma which is obtained from centrifuged whole blood that has been treated with an effective amount of anti-clotting agent and separated into the three different components of the platelet-poor plasma, the platelet-rich plasma, and the red blood cells. The platelet-rich plasma is treated with calcium chloride to reverse the action of the anti-clotting agent, apparently permitting clotting. See, for example, Britton paragraphs [0040] *et seq*.

Accordingly, in Britton the platelet-rich plasma which apparently has been permitted to clot by the blood clotting function of fibrinogen in plasma, is attached to a bandage, and the resultant product can be topically administered so as to heal a wound.

In contrast, as noted above, Applicants recited process in independent claim 105 is directed to a method for preparing a wound-healing promoting material which comprises extracorporeally contacting at least living leukocytes contained in a liquid portion with a sheet-shaped porous body to trap the at least living leukocytes on surfaces of pores of the porous body, and substantially not trapping the liquid portion including fibrinogen on the surfaces.

Thus, at least certain components, such as at least living leukocytes contained in a liquid portion can be trapped on the surfaces of the sheet-shaped porous body without substantially trapping the liquid portion including fibrinogen, and thereby preparing a wound-healing promoting material without using blood clotting function of fibrinogen.

One having ordinary skill in the art would not have combined the disclosures of Read and Britton in view of their different disclosures related to fixed-dried platelets in Read and the use of the platelet-rich plasma in Britton. However, even if for the sake of argument the disclosures were combined, Applicants' claimed subject matter would not be at hand, because neither of Read nor Britton discloses a method for preparing a wound-healing promoting material as recited by Applicants that amongst the feature recited in the claims includes at least living leukocytes contained in a liquid portion being trapped on the surfaces of the sheet-shaped porous body without trapping the liquid portion including fibrinogen.

Wakelyn is used in the rejections solely to try and establish that the woven or nonwoven cotton inherently has pores. Whether or not this is the situation, Wakelyn does not overcome any of the above-noted deficiencies of Read or Read and Britton.

Faraday is used in the rejections merely in an attempt to try and establish that leukocytes in Britton would be living. However, the rejection contends that Britton only uses centrifugation of whole blood to isolate the platelet-rich plasma with leukocytes so the leukocytes are inherently living. However, the rejection does not address that Britton discloses the use of an anti-clotting agent, and the subsequent use of calcium chloride. The Examiner is reminded that in order for inherency to be present the indicated result must necessarily be present. However, the rejection has not established that leukocytes in Britton will be inherently alive. Accordingly, the rejections are deficient for at least this additional reason.

Further, the Office Action alleges that certain dependent claims are obvious based further upon Seagull, Onodera in light of support from Jan. In these rejections, only Onodera is used in the rejections for its disclosure of leukocytes. In this regard, Seagull is only used in an attempt to try and establish obviousness of Applicants' recited fiber diameters; Jan is used in an attempt to establish , "This charge injection would inherently exclude erythrocytes since their surface is negatively changed and thus repelled by a negative surface charge as supported by Jan (introduction, 1st paragraph)".

Applicants submit that whether or not it would be been obvious to combine Seagull with the other documents used in the rejections or that Jan establishes inherency as asserted in the rejection, Applicants' claimed subject matter would not be at hand. Any combination of the disclosures would not have arrived at Applicants' subject matter as recited in independent claim 105 and further patentably defined in the dependent claims.

Moreover, Onodera discloses trapping of blood components, such as platelets and leukocytes. However, Onodera discloses removing components from blood, and not for arriving at the preparation of a wound-healing promoting material.

For example, attention is once again directed to the Summary of the Invention section of Onodera, wherein it is disclosed that:

> The present inventors have made extensive and intensive studies with a view toward developing a filter medium which is capable of suppressing an increase in the bradykinin concentration of a blood material when the blood material is contacted with the filter medium for treatment of the blood material, so that even when the treated blood material is returned to a recipient, the recipient will not suffer from anaphylactic reactions caused by an increased bradykinin concentration. As a result of these studies, it has unexpectedly been found that the conventional filter media, which have a large quantity of negative charge introduced for improving the wettability thereof with blood, are likely to cause an increase in the bradykinin concentration of the blood material when they are used for treating the blood material, frequently leading to the occurrence of anaphylactic symptoms, that when the concentration of bradykinin in plasma of blood is increased to a level of 4,000 pg/ml or more of the plasma, serious anaphylactic symptoms are likely to occur, and that when a filter medium having a surface electric charge of not smaller than -30 μeq/g of the filter medium is used for treating blood, an increase in bradykinin content of the blood upon being contacted with the filter medium can be suppressed to maintain the bradykinin concentration in the blood at a level well below 4,000 pg/ml of the plasma of the blood, so that occurrence of serious anaphylactic symptoms is successfully prevented. The present invention has been completed, based on such novel findings.
>
> Accordingly, it is an object of the present invention to provide a filter medium for treating a blood material, which can satisfactorily suppress an increase in bradykinin concentration of a blood material upon being contacted with the blood material.
>
> It is another object of the present invention to provide a filter medium free of the bradykinin problem, for use in removing leukocytes from a leukocyte-containing suspension, including whole blood.
>
> It is still another object of the present invention to provide a filter membrane free of the bradykinin problem, for use in separating an undesired substance from whole blood or plasma.
>
> It is a further object of the present invention to provide an adsorptive composite type filter medium free of the bradykinin problem, for use in removing an undesired substance from whole blood or plasma.
>
> It is still a further object of the present invention to provide an apparatus for treating a blood material having packed therein a filter medium for removing leukocytes from a leukocyte-containing suspension or having packed therein an adsorptive composite type filter medium for removing an undesired substance from whole blood or plasma.

Thus, Read discloses that dried-fixed platelets are used according to his invention, and Onodera discloses treatment of blood for removing components so that the blood can be returned to the body. Certainly, one having ordinary skill in the art would not have been motivated to combine the diverse disclosures of Read and Onodera. Moreover, Read specifically discloses the use of fixed-dried platelets to form his surgical aid, and one having ordinary skill in the art would not have been motivated to combine the disclosure of Onodera to separate blood components with the forming of surgical aids disclosed by Read. The Examiner is reminded that there must be a reason why one having ordinary skill in the art would have combined the diverse disclosures of Read and Onodera. In the instant situation there is no reason outside Applicants' disclosure to arrive at Applicants' claimed subject matter.

Moreover, Applicants note that that the present invention provides a number of advantages. These advantages cannot be achieved by using fixed-dried platelets as disclosed by Read, and are not taught or suggested by any combination of the prior art used in the rejections of record. Thus, the present invention has at least the advantageous effects, as follows:

(1) Growth factor which is produced by leucocytes contributes to the promotion of cell growth ability in tissue and the regeneration of the tissue.

(2) Growth factor which is produced by a living cell acts on this living cell per se (self-secretion), and more strong action is obtained. Further, growth factor which is produced from the adjacent cells and is diffused acts on (paracrine system), and thus effects are enhanced intercellularly.

(3) Leucocytes from peripheral blood promote neoangiogenesis and produce new blood flow. Thus, wound-healing is promoted.

(4) The monocyte fraction in peripheral blood is differentiated into cells such as epithelial cell, vascular endothelial cell, liver cell, and nerve cell, and is expected to show wound-healing effect.

Still further, Applicants once again point out that claim 120 is directed to a wound-healing promoting material which is obtained by the method for preparing a wound-healing promoting material according to claim 105. For at least the reasons set forth above, claims 120 is allowable over any combination of the documents used in the rejections of record.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the restriction requirement and rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wishes to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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